

What is claimed is:

1. A method for administering nucleic acid to provide a polypeptide in cells in tissue of interest, comprising:
treating the tissue with a phosphodiesterase inhibitor compound; and
administering exogenous nucleic acid to the tissue.
2. The method of claim 1 wherein the tissue is treated with the phosphodiesterase inhibitor compound to increase vascular permeability.
3. The method of claim 1 or 2 wherein the tissue is treated with a further agent distinct from the phosphodiesterase inhibitor compound to increase vascular permeability.
4. The method of any one of claims 1 through 3 wherein the nucleic acid is administered under low calcium ion concentration conditions.
5. The method of any one of claims 1 through 4 wherein the tissue is treated with a low calcium ion concentration solution.
6. A method of any one of claims 1 through 5 wherein the nucleic acid is administered by perfusion.
7. The method of claim 6 wherein the perfusate of nucleic acid is recirculated and then readministered through the organ or cell mass.
8. The method of any one of claims 1 through 7 wherein the permeability agent in addition to the phosphodiesterase compound is administered and that permeability agent is serotonin, bradykinin, platelet-activating factor, prostaglandin E₁, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine or L-N-nitro-arginine methyl ester.

9. The method of claim 8 wherein additional permeability agent exhibits at least about 5% of the permeability activity of bradykinin in a standard permeability assay.

10. The method of any one of claims 1 through 10 wherein the phosphodiesterase inhibitor compound is perfused through vasculature of the tissue prior to administration of the nucleic acid.

11. The method of any one of claims 1 through 10 wherein a low calcium ion concentration solution is perfused through vasculature of the tissue prior to administration of the nucleic acid.

12. The method of any one of claims 1 through 11 wherein low calcium ion concentration conditions are provided by perfusing through vasculature of the tissue a fluid having a calcium ion concentration of less than about 500 $\mu\text{mol/L}$.

13. The method of any one of claims 1 through 12 wherein the nucleic acid is administered as a viral vector in a solution at a concentration of about 1×10^8 pfu/ml or greater.

14. The method of any one of claims 1 through 13 wherein the nucleic acid is administered to a solid cell mass.

15. The method of any one of claims 1 through 13 wherein the nucleic acid is administered to a solid organ.

16. The method of any one of claims 1 through 13 wherein the nucleic acid is administered to cells of heart, lung, kidney, testes, ovaries, skeletal muscle, kidneys, brain or spleen.

17. The method of any one of claims 1 through 15 wherein the tissue is cardiac tissue.

18. The method of any one of claims 1 through 15 wherein the tissue is liver tissue.

19. The method of any one of claims 1 through 18 wherein the tissue comprises malignant cells.

20. The method of any one of claims 1 through 19 wherein the nucleic acid is administered to a solid tumor.

21. The method of any one of claims 1 through 20 wherein the tissue is mammalian.

22. The method of any one of claims 1 through 21 wherein the nucleic acid is administered *ex vivo*.

24. The method of any one of claims 1-22 wherein the nucleic acid is administered *in vivo*.

25. The method of any one of claims 1-24 wherein the nucleic acid is administered to a human.

26. The method of any one of claims 1-24 wherein the nucleic acid is administered to livestock, poultry or dog or cat.

27. A method for producing a gene product in malignant cells or proximate to malignant cells in targeted tissue, comprising:

treating the tissue with a phosphodiesterase inhibitor compound; and
administering exogenous nucleic acid to the tissue.

28. The method of claim 27 wherein the phosphodiesterase inhibitor compound treatment increases vascular permeability of the treated tissue.

29. The method of claims 27 or 28 wherein the nucleic acid is administered under low calcium ion concentration conditions.

30. The method of any one of claims 27 through 29 wherein a solid tumor comprises the malignant cells.

31. The method of any one of claims 27 through 30 wherein the malignant cells are present in a lung, liver, prostate, brain, testes or ovaries of a subject.

32. The method of any one of claims 27 through 31 wherein the nucleic acid is administered by perfusion.

33. The method of any one of claims 27 through 32 wherein the nucleic acid is administered to a mammal.

34. The method of any one of claims 27 through 32 wherein the nucleic acid is administered to a primate.

35. The method of any one of claims 27 through 32 wherein the nucleic acid is administered to a human.

36. A method of providing, to a recipient subject, donor cells that comprise nucleic acid exogenous to the cells, comprising:

treating tissue comprising the donor cells with a phosphodiesterase compound to increase vascular permeability of exogenous nucleic acid;
administering nucleic acid to the tissue; and

introducing the donor cells into the recipient subject to provide a gene product of the nucleic acid.

37. The method of claim 36 wherein an organ comprising the donor cells is transplanted into the recipient subject.

38. The method of claim 36 wherein the donor cells are swine cells or primate cells.

39. The method of any one of claims 36 through 38 wherein the tissue is treated with a vascular permeability agent distinct from the phosphodiesterase compound to increase vascular permeability.

40. The method of any one of claims 36 through 39 wherein the tissue is treated with a low calcium ion concentration solution to increase vascular permeability.

41. The method of any one of claims 36 through 40 wherein the nucleic acid is administered under low calcium ion concentration conditions.

42. The method of any one of claims 36 through 42 wherein the gene product reduces recognition of the donor cells by the immune system of the recipient subject.

43. The method of any one of claims 36 through 42 wherein the donor cells are introduced into a mammal.

44. The method of any one of claims 36 through 43 wherein the donor cells are introduced into a human.

45. The method of any one of claims 1 through 44 wherein the phosphodiesterase inhibitor compound is sildenafil, zaprinast or T-1032.

46. The method of any one of claims 1 through 44 wherein the phosphodiesterase inhibitor compound is represented by any one of Formula I through XII as those formulae are set forth above.

46. A method of any one of claims 1 through 45 wherein an activator of nitric oxide or cGMP is administered.

47. A method of any one of claims 1 through 46 wherein VEGF, nitroglycerin, nitroprusside or 8-Br-cGMP is administered.

48. A method for administering nucleic acid to provide a polypeptide in cells in tissue of interest, comprising:

treating the tissue with an an activator of nitric oxide or cGMP; and
administering exogenous nucleic acid to the tissue.

49. A pharmaceutical kit comprising:
a permeability agent that comprises a phosphodiesterase inhibitor compound;
and nucleic acid for administration to a subject.

50. The kit of claim 49 further comprising a solution having a calcium ion concentration of less than about 500 $\mu\text{mol/L}$.

51. The kit of claim 49 or 50 further comprising a device for delivery of the nucleic acid.

52. The kit of claim 51 wherein the delivery device is a catheter.

53. The kit of any one of claims 49 through 52 wherein the nucleic acid is present in the kit as a viral vector.

54. The kit of any one of claims 49 through 53 wherein the kit further comprises a permeability agent in addition to the phosphodiesterase inhibitor compound.

55. The kit of any one of claims 49 through 54 wherein the kit comprises an activator of nitric oxide or cGMP.

56. The kit of claim 54 or 55 wherein the additional permeability agent is serotonin, bradykinin, VEGF, platelet-activating factor, prostaglandin E₁, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine, L-N-nitro-arginine methyl ester, nitroglycerin, nitroprusside or 8-Br-cGMP.

57. A treatment solution comprising:

- a) a phosphodiesterase inhibitor compound; and
- b) nucleic acid.

58. The treatment solution of claim 57 wherein the solution has a low calcium ion concentration.

59. The treatment solution of claim 57 wherein the solution has a calcium ion concentration of less than about 500 $\mu\text{mol/L}$.

60. The treatment solution of any one of claims 57 through 59 wherein the treatment solution further comprises a permeability agent in addition to the phosphodiesterase inhibitor compound.

61. The treatment solution of any one of claims 57 through 60 wherein the treatment solution comprises an activator of nitric oxide or cGMP.

62. The treatment solution of claim 60 wherein the additional permeability agent is serotonin, bradykinin, VEGF, platelet-activating factor, prostaglandin E₁, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine, L-N-nitro-arginine methyl ester, nitroglycerin, nitroprusside or 8-Br-cGMP.

63. A treatment solution comprising nucleic acid in a fluid carrier and a phosphodiesterase inhibitor compound.

64. A treatment solution of claim 63 wherein the kit further comprises a permeability agent in addition to the phosphodiesterase inhibitor compound.

65. The treatment solution of claim 63 or 64 wherein the kit comprises an activator of nitric oxide or cGMP.

66. The treatment solution of claim 63 wherein the additional permeability agent is serotonin, bradykinin, VEGF, platelet-activating factor, prostaglandin E₁, histamine, vascular endothelium growth factor, zona occludens toxin, interleukin-2, plasma kinins, L-N-monomethyl arginine, L-N-nitro-arginine methyl ester, nitroglycerin, nitroprusside or 8-Br-cGMP.

67. The treatment solution of any one of claims 63 through 66 wherein the solution has a calcium ion concentration of less than about 500 µmol/L.

68. A solution of any one of claims 63 through 67 wherein the solution is pharmaceutically acceptable.

69. A solution of any one of claims 57 through 68 wherein the solution comprises one or more therapeutic agents in addition to the nucleic acid.